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(71) Applicant (*for all designated States except US*): **PFIZER PRODUCTS INC.** [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **COLBERG, Juan Carlos** [US/US]; Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340 (US). **DONADELLI, Alessandro** [IT/IT]; ACS Dobfar S.p.A., Viale Addetta 6/8/10, I-20067 Tribiano (IT). **FOGLIATO, Giovanni** [IT/IT]; ACS Dobfar S.p.A., Viale Addetta 6/8/10, I-20067 Tribiano (IT). **ZENONI, Maurizio** [IT/IT]; ACS Dobfar S.p.A., Viale Addetta 6/8/10, I-20067 Tribiano (IT).

(74) Agents: **LUMB, J., Trevor** et al.; Pfizer Inc., 201 Tabor Road, Morris Plains, NJ 07950 (US).

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(54) Title: COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPHORINS

(57) Abstract: This invention relates to a novel process for the preparation of 3-cyclic-ether-substituted cephalosporins of formula (I): wherein the group CO_2-R^1 is a carboxylic acid or a carboxylate salt and R2 has the formula (a): wherein A^1 is selected form the group consisting of C_{6-10}aryl, C_{1-10}heteroaryl and C_{1-10}heterocyclyl; A^2 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{6-10}aryl C_{1-6}alkyl(CO)(C_{1-6})alkyl-O-, HO(CO)(C_{1-6})alkyl, mono-(C_{6-10}aryl)(C_{1-6}alkyl), di-(C_{6-10}aryl)(C_{1-6}alkyl) and tri-(C_{6-10}aryl)(C_{1-6}alkyl); from a zwitterionic compound of formula (II), or from a compound of formula (V): wherein R^2 is as defined above and R^3 is para-nitrobenzyl or allyl. The invention also relates to the preparation of the above compounds of formula (II) and (V).

COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS

Background of the Invention

This invention relates to a novel process for the preparation of 3-cyclic-ether-substituted cephalosporins. The invention also relates to novel processes for preparing zwitterions, para-nitrobenzyl esters and allyl esters useful in the preparation of the above cephalosporins. The invention also relates to 3-cyclic-ether-substituted cephalosporins. These compounds possess certain advantageous properties, such as crystalline form and high enantiomeric excess (e.e.).

The 3-cyclic-ether-substituted cephalosporins prepared by the methods of the present invention have prolonged and high levels of antibacterial activity and possess good absorption parentally in humans and animals. The 3-cyclic-ether-substituted cephalosporins prepared by the processes of the present invention contain a cyclic ether substituent at carbon 3 of the cephalosporin nucleus.

GB 1405758 describes alternative methods of preparation of certain 3-cyclic-ether-substituted cephalosporins.

J. Antibiotics (1994), vol. 47(2), page 253, and WO 92/01696 also describe alternative methods of preparation of compounds of formula **I**, as defined herein below, and compounds useful in said processes.

United States Patents No. 6,020,329 and 6,077,952 describe salts, polymorphs, solvates and hydrates of 3-cyclic-ether-substituted cephalosporins.

United States Patent No. 6,001,997 describes alternative methods of preparations of 3-cyclic-ether-substituted cephalosporins.

United States Provisional Patent Application entitled “Process and Ester Derivatives Useful For Preparation of Cephalosporins”, filed November 30, 2000, refers to intermediates and processes to prepare 3-cyclic-ether-substituted cephalosporins.

Each of the above referenced publications, patents and patent applications is hereby incorporated by reference in its entirety.

The present inventors have discovered a novel compound of formula **I**, as defined herein below. The present inventors have also discovered a high-yielding process for the preparation of said compounds of formula **I**.

Suitable solvents for the aforesaid process of conversion of compounds of formula **II** into compounds of formula **I** of the invention include water, acetone, tetrahydrofuran, ethyl acetate, dimethylacetamide, dimethylformamide, acetonitrile, methylene chloride, 1,2-dichloroethane or mixtures thereof. In one embodiment of the invention, the solvent is tetrahydrofuran. In another embodiment of the invention, the solvent is ethyl acetate. Preferably, the solvent is water, acetone or mixtures thereof. More preferably the solvent is a mixture of acetone and water. Most preferably the solvent is a 1.3:1 mixture of acetone and water.

Suitable bases for the aforesaid conversion of the invention include diisopropylethylamine or sodium hydroxide. Preferably, the base is sodium hydroxide, most preferably 15% aqueous sodium hydroxide.

Suitable coupling agents for the aforesaid conversion of the invention include N,N'-diethylcarbodiimide, N,N'-dipropyl carbodiimide, N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide, N-ethyl-N'-[3-(dimethylamino)propyl]carbodiimide, N,N'-carbonyldiimidazole or N,N'-carbonyldithiazole. A preferred coupling agent is N,N'-dicyclohexylcarbodiimide. Preferably, the aforesaid conversion is conducted in the absence of any coupling agents.

Suitable catalysts for the aforesaid conversion of the invention include Lewis acids. Suitable Lewis acids are selected from the group consisting of boron trihalide, such as boron tribromide, and aluminum halide, such as aluminum chloride. Preferably, the aforesaid conversion is conducted in the absence of any catalysts.

The aforesaid conversion of the invention can be conducted at a temperature of about -40°C to about +30°C, preferably about +20°C to about +30°C. The aforesaid process can be conducted for a period from about 1 hour to about 24 hours; preferably about 3 hours.

Suitable leaving groups L of the aforesaid compound of formula **III** of the aforesaid conversion include hydroxy, halo, azido, mono(C_{1-6}alkyl)carbonate, (C_{1-6}alkyl)carboxylate, (C_{6-10}aryl)carboxylate, mono-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di(C_{1-6}alkyl)phosphorothioate, (C_{1-6}alkyl)sulfonyl, mono-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, di-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, (C_{1-6}alkyl)-(CO)-S-, cyano-C_{1-6}alkoxy, C_{6-10}aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy or N-oxy-succinimidyl.

In one embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of hydroxy, halo and azido.

In another embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of mono(C_{1-6}alkyl)carbonate, (C_{1-6}alkyl)carboxylate, (C_{6-10}aryl)carboxylate,

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched moieties or combinations thereof. alkyl groups, wherever they occur, may be optionally substituted by a suitable substituent.

The term "cycloalkyl", as used herein, unless otherwise indicated, includes a mono or bicyclic carbocyclic ring (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl and bicyclo[5.2.0]nonanyl, etc.); optionally containing 1or 2 double bonds and optionally substituted by 1 to 3 suitable substituents as defined below such as fluoro, chloro, trifluoromethyl, (C_{1-4})alkoxy, (C_{6-10})aryloxy, trifluoromethoxy, difluoromethoxy or (C_{1-4})alkyl, more preferably fluoro, chloro, methyl, ethyl and methoxy.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is as defined above.

The term "halo", as used herein, unless otherwise indicated, includes fluorine, chlorine, bromine or iodine, preferably bromine or chlorine.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one or more hydrogen(s), such as phenyl or naphthyl, optionally substituted by 1 to 3 suitable substituents such as fluoro, chloro, cyano, nitro, trifluoromethyl, (C_{1-6})alkoxy, (C_{6-10})aryloxy, (C_{3-8})cycloalkyloxy, trifluoromethoxy, difluoromethoxy or (C_{1-6})alkyl.

The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one or more hydrogen(s), such as benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl, wherein said (C_{1-10})heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or two substituents independently selected from F, Cl, Br, CN, OH, (C_{1-4})alkyl, (C_{1-4})perfluoroalkyl, (C_{1-4})perfluoroalkoxy, (C_{1-4})alkoxy and (C_{3-8})cycloalkyloxy. The foregoing groups, as derived from the compounds listed above, can be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole can be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached).

The term "heterocyclyl", as used herein, unless otherwise indicated, includes an organic radical derived from a non-aromatic heterocyclic compound by removal of one or more hydrogens, such as 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]-heptanyl, azetidinyl,

and stereoisomers of the compounds of formula **I** and mixtures thereof. The compounds of the invention also exist in different tautomeric forms. This invention relates to all tautomers of formula **I**. Those skilled in the art are well aware that the cephalosporin nucleus exists as a mixture of tautomers in solution. The various ratios of the tautomers in solid and liquid form is dependent on the various substituents on the molecule as well as the particular crystallization technique used to isolate a compound.

Preferably, the group OA^2 of said compounds of formula **III** is cis to the amide linkage, i.e., the Z-configuration is preferred.

Suitable deprotecting agents for the aforesaid process of conversion of compounds of formula **V** into compounds of formula **I** of the invention include sodium dithionite or tetrakis triphenyl phosphine palladium (0).

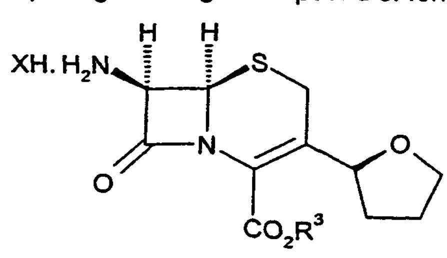
Suitable solvents for the aforesaid conversion include acetone, water, tetrahydrofuran, methylene chloride or mixtures thereof. In one embodiment of the invention, the solvent is methylene chloride, tetrahydrofuran or mixtures thereof. In another embodiment of the invention, the solvent is tetrahydrofuran. In a preferred embodiment of the aforesaid conversion of the invention, the solvent is methylene chloride.

The aforesaid conversion may be conducted at a temperature of about 0°C to about 45°C. The aforesaid conversion may be conducted for a period from about 1 hour to about 24 hours.

In one embodiment of the aforesaid conversion, R^3 is para-nitrobenzyl. Within, this embodiment, suitably the deprotecting agent is sodium dithionite. Within this embodiment, suitably the aforesaid conversion is conducted at a temperature of about 40°C. Within this embodiment, suitably the aforesaid process is conducted for about 4 hours.

In a preferred embodiment of the aforesaid conversion, R^3 is allyl. Within this embodiment, the preferred deprotecting agent is tetrakis triphenyl phosphine palladium (0). Within this embodiment, the aforesaid process is conducted at a temperature of about 20°C to about 35°C; preferably about 27°C to about 30°C. Within this embodiment, preferably the aforesaid process is conducted for about 5 hours.

The present invention also includes a process for the preparation of the above compound of formula **II** comprising reacting a compound of formula **IV**



IV

boron trihalide, such as boron tribromide, or aluminum halide, such as aluminum chloride. Preferably, the aforesaid conversion is conducted in the absence of any catalysts.

The aforesaid conversion may be conducted at a temperature of about -40°C to about +40°C. The aforesaid conversion may be conducted for a period of from about 1 hour to about 24 hours.

In one embodiment of the aforesaid conversion of the invention, R^3 is para-nitrobenzyl. Within this embodiment, suitably the aforesaid conversion is conducted at a temperature of about +20°C to about +30°C. Within this embodiment, suitably the aforesaid conversion is conducted for about 3 hours.

In a preferred embodiment of the aforesaid conversion of the invention, R^3 is allyl. Within this embodiment, preferably the solvent is methylene chloride. Within this embodiment, preferably the aforesaid conversion is conducted at a temperature of about 20°C to about 40°C. Within this embodiment, preferably the aforesaid conversion is conducted for about 24 hours.

Suitably the leaving group L of the compound of formula **III** in the aforesaid conversion of the invention includes hydroxy, halo, azido, mono(C_{1-6}alkyl)carbonate, (C_{1-6}alkyl)carboxylate, (C_{6-10}aryl)carboxylate, mono-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di(C_{1-6}alkyl)phosphorothioate, (C_{1-6}alkyl)sulfonyl, mono-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, di-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, (C_{1-6}alkyl)-(CO)-S-, cyano-C_{1-6}alkoxy, C_{6-10}aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy or N-oxy-succinimidyl.

In one embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of hydroxy, halo and azido.

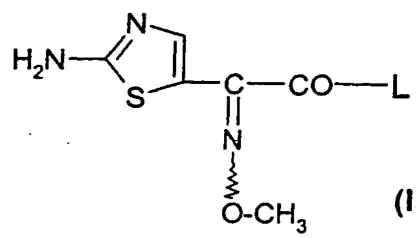
In another embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of mono(C_{1-6}alkyl)carbonate, (C_{1-6}alkyl)carboxylate, (C_{6-10}aryl)carboxylate, mono-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate and di(C_{1-6}alkyl)phosphorothioate.

In yet another embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of (C_{1-6}alkyl)sulfonyl, mono-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, di-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl and (C_{1-6}alkyl)-(CO)-S-.

In yet another embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of cyano-C_{1-6}alkoxy, C_{6-10}aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy and N-oxy-succinimidyl.

In other generic or sub-generic embodiments of the invention, the A^2 moiety of said R^2 is hydrogen or C_{1-6}alkyl. A preferred embodiment of the invention includes each of the foregoing generic and sub-generic embodiments wherein the A^2 moiety of said R^2 is C_{1-6}alkyl, more preferably methyl.

In a preferred embodiment of each of the foregoing generic and sub-generic embodiments the invention, a compound of the formula **III** has a formula **IIIa**



(IIIa)

wherein L is a leaving group, such as halo, methanesulfonyl, dialkylphosphorothioate, such as diethylphosphorothioate or 3-benzthiazolyloxy.

In a most preferred embodiment of each of the foregoing embodiments of the invention, a compound of the formula **III** has a formula **IIIa**, as defined above, wherein L is diethylphosphorothioate or acetate.

The optional conversion of R^2 to a different R^2 and the optional formation of a pharmaceutically acceptable salt, can be carried out using methods well known in the art.

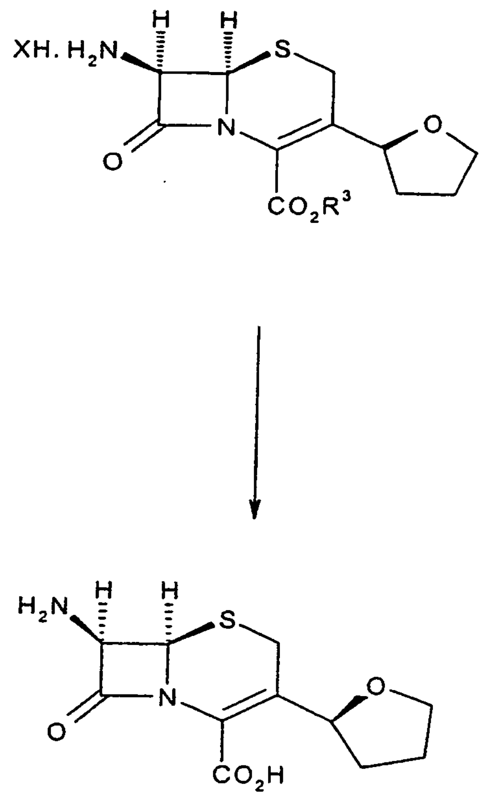
In the processes described hereinabove and hereinbelow, it may be necessary to remove protecting groups. Deprotection can be carried out by any convenient method known in the art such that unwanted side reactions are minimized. Separation of unwanted by-products can be carried out using standard methods known to those skilled in the art (for example, see "Protection of the Amino Group", in *Protective Groups in Organic Synthesis*, 2nd Edition, T. W. Greene and P.G. M. Wuts, Ed., Wiley and Sons, Inc. 1991, pp. 309-405).

The present invention also relates to a method of using a zwitterion intermediate for the preparation of 3-cyclic-ether-substituted cephalosporins.

<u>Detailed Description of the Invention</u>

The process of the present invention and the preparation of the compound of the present invention are illustrated in the following reaction schemes. Except where otherwise indicated, in the reaction schemes and discussion that follow, substituents R^1, R^2, R^3, L, A^1, A^2 and X are as defined above unless otherwise described.

SCHEME 2



IV

II

Scheme 1 refers to the preparation of compounds of formula I. Referring to Scheme 1, a compound of formula I can be prepared by reacting a compound of formula II with a compound of formula III

R^2-L (III);

wherein L is a leaving group, in the presence of a base and a solvent.

Suitable leaving groups include hydroxy, halo, azido, mono(C_{1-6}alkyl)carbonate, (C_{1-6}alkyl)carboxylate, (C_{6-10}aryl)carboxylate, mono-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di(C_{1-6}alkyl)phosphorothioate, (C_{1-6}alkyl)sulfonyl, mono-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, di-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, (C_{1-6}alkyl)-(CO)-S-, cyano-C_{1-6}alkoxy, C_{6-10}aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy or N-oxy-succinimidyl. Preferably, the leaving group is di(C_{1-6}alkyl)phosphorothioate, such as diethylphosphorothioate.

Suitable bases include diisopropylethylamine or sodium hydroxide, preferably sodium hydroxide, most preferably 15% aqueous sodium hydroxide.

Suitable solvents include water, acetone, tetrahydrofuran, ethyl acetate, dimethylacetamide, dimethylformamide, acetonitrile, methylene chloride, 1,2-dichloroethane, or mixtures thereof; preferably a mixture of water and acetone, most preferably a mixture of 1:1.3 of water and acetone.

The aforesaid reaction can be conducted at a temperature of about -40°C to about 30°C; preferably about 20°C to about 30°C. The aforesaid reaction can be conducted for a period from about 1 hour to about 24 hours, preferably for about 3 hours.

Optionally, the aforesaid reaction can be effected in the presence of an acid binding agent, for example a tertiary amine (such as triethylamine), pyridine (such as 2,6-lutidine or 4-dimethylaminopyridine), or dimethylaniline. Optionally, the aforesaid reaction can also be carried out in the presence of molecular sieves, an inorganic base (such as calcium carbonate or sodium bicarbonate) or an oxirane, which binds the hydrogen gas liberated in the aforesaid reaction. The oxirane is preferably C_{1-6}alkyl-1,2-alkylene oxide, such as ethylene oxide or propylene oxide.

Optionally, the aforesaid reaction can be conducted in the presence of a coupling agent. Suitable coupling agents include N,N'-diethylcarbodiimide, N,N'-dipropyl carbodiimide, N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide, N-ethyl-N'-[3-(dimethylamino)propyl]carbodiimide, N,N'-carbonyldiimidazole, and N,N'-carbonyldithiazole. Preferably, the coupling agent is N,N'-diethylcarbodiimide. Preferably the reaction is conducted in the absence of any couplings agents.

Optionally, the aforesaid reaction can be conducted in the presence of a catalyst. Suitable catalysts include a Lewis acid, such as boron trihalide or aluminum halide. Preferably the reaction is conducted in the absence of any catalysts.

Scheme 3 refers to an alternative process of preparation of a compound of formula **I**. Referring to Scheme 3, a compound of formula **I** can be prepared by reacting a compound of formula **V**, wherein R^3 is preferably allyl; with a suitable deprotecting agent in a solvent.

Suitable deprotecting agents include sodium dithionite or tetrakis triphenyl phosphine palladium (0).

Suitable solvents include acetone, water, tetrahydrofuran, methylene chloride or mixtures thereof. Preferably the solvent is methylene chloride.

The aforesaid reaction can be conducted at a temperature of about 0°C to about 45°C. The aforesaid reaction can be conducted for a period from about 1 hour to about 24 hours.

A compound of formula **V** can be prepared by reacting a compound of formula **IV**, wherein R^3 is preferably allyl; and X is preferably chloro; with a compound of formula **III**

$$R^2\text{-}L \qquad \text{(III)}$$

in a solvent.

Suitable solvents for the aforesaid reaction include methylene chloride, tetrahydrofuran or mixtures thereof. Preferably, the solvent is methylene chloride.

Optionally, the aforesaid reaction can be conducted in the presence of a coupling agent. Suitable coupling agents include N,N'-diethylcarbodiimide, N,N'-dipropyl carbodiimide, N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide, N-ethyl-N'-[3-(dimethylamino)propyl]carbodiimide, N,N'-carbonyldiimidazole, or N,N'-carbonyldithiazole. Preferably, the coupling agent is N,N'-diethylcarbodiimide. Preferably the aforesaid reaction is conducted without any coupling agents.

Optionally, the aforesaid reaction can be conducted in the presence of a catalyst. Suitable catalysts include a Lewis acid, such as boron trihalide or aluminum halide. Preferably the aforesaid reaction is conducted without any catalysts.

The aforesaid reaction can be conducted at a temperature of about -40°C to about +40°C, preferably about +20°C to about +40°C. The aforesaid reaction can be conducted for a period from about 1 hour to about 24 hours; preferably about 24 hours.

A compound of formula **IV** can be prepared as described above in the description for Scheme 2.

Compounds of this invention can be crystallized or recrystallized from solvents such as organic solvents. In such cases solvates can be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that can be produced by processes such as lyophilization.

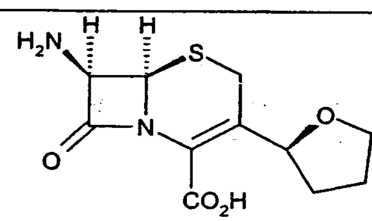
The compounds of formula **(I)** are useful for the preparation of a 3-cyclic-ether-substituted cephalosporin, i.e., the active compound. The active compound possesses activities against gram positive and gram negative bacteria. Methods for assaying

METHOD B: FROM ALLYL-7-(2-(2-AMINOTHIAZOL-4-YL)-2-METHOXYIMINO)-3-TETRAHYDROFURAN-2-YL)-8-OXO-5-THIA-1-AZA-BICYCLO[4.2.0]OCT-2-ENE-2-CARBOXYLATE, BENZENE SULPHINIC ACID SALT

To a 10-liter glass vessel was charged methylene chloride (4.50 liters) followed by tetrakis(triphenylphospine) palladium (9.0 g, 7.8 mmoles) in nitrogen atmosphere. Triphenylphosphine (1.0 g, 3.8 mmoles) was added and stirred into the solution. Allyl-7-(2-(2-aminothiazol-4-yl)-2-methoxyimino)-3-tetrahydrofuran-2-yl)-8-oxo-5-thia -1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate, benzene sulphinic acid salt (225.0g, 354 mmoles) was charged and warmed to 27-30°C. The reaction was monitored by HPLC, and further additions of catalyst was made as required. On completion, the solid product was filtered and washed twice with methylene chloride (700 ml total). The yellow to tan product was then air dried to achieve a constant weight before storage in a freezer. The yields range from 49-110.1%.

Example 2

7-Amino-8-oxo-3-(tetrahydrofuran-2-yl)-5-thia-1-aza-bicyclo[4.2.0]octa-1(6),2,4-triene-2-carboxylic acid

No.	Structure	Molecular Weight
2	 II	270.29

7-Amino-8-oxo-3-(tetrahydrofuran-2-yl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene -2-carboxylic acid 4-nitro-benzyl ester (20 g, 54 mmol), water (30 ml) and acetone (90 ml) were combined to form a slurry. The pH of the slurry was adjusted to 7 by using aqueous ammonia solution (15%). To the resulting solution was added sodium hydrosulfite (32 g, 3.8 equiv.) in water (40 mL) solution. The pH of the resulting solution was adjusted to 7 by using aqueous ammonia (15%) while maintaining the temperature between 40°C to 45°C. After stirring for 1 hour at 45°C, the pH was re-adjusted to 3.5 with a hydrochloric acid aqueous solution (15%). The resulting slurry was granulated, filtered and dried to afford the title compound (11.3 g, 80%).

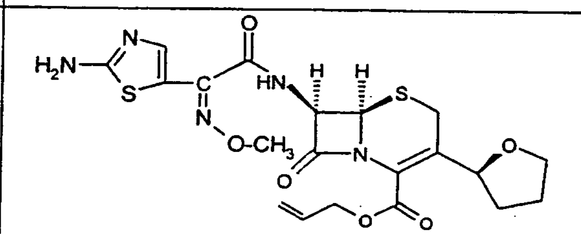
Preparation 1: (3-Benzyl-7-oxo-4-thia-2,6-diaza-bicyclo[3.2.0]hept-2-en-6-yl)-hydroxy-acetic acid-4-nitro-benzyl ester

Isopropanol (500 mL), methylene chloride (1800 mL) and (1R)-(4-nitrophenyl)methyl ester-α,1-methylethylidene)-7-oxo-3-(phenylmethyl)-4-thia-2,6-diazabicyclo[3.2.0]hept-2-ene

addition of phosphorus pentachloride (104 g, 0.5 mol). α-Picoline (92 ml) in dichloromethane (60 ml) solution was added while maintaining the temperature between -40°C to 30°C. The mixture was stirred for 1 hour followed by the addition of isopropanol (660 ml). The reaction mixture was warmed to 22°C, granulated, filtered and dried to give the title compound (250 g, 45%).

Example 3

Allyl-7-(2-(2-Aminothiazol-4-yl)-2-methoxyimino)-3-tetrahydrofuran-2-yl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate, benzene sulphinic acid salt

No.	Structure	Molecular Weight
3		493.56 (634.62 as benzene sulphinic acid salt)

Preparation 1: Allyl-7-phenylacetamido-3-(tetrahydrofuran-2-yl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]-oct-2-ene-2-carboxylate

To a 100-liter glass vessel was added toluene (47 liters) and allyl-2-tri-n-methylphosphororanylidene-2-(3-phenylacetamido-4-(tetrahydrofuran-2 -ylcarbonyl-methylthio)azetidin-on-1yl)acetate (1990 g). The solution was purged with nitrogen and brought to reflux. Any water present was collected and the solution was refluxed for 20 hours. After sampling for TLC/HPLC analysis, the solution was cooled back to ambient temperature. The solution was then run through Silica Gel 60 (4.5 kg), with the silica being further eluted with additional toluene (33 liters). The toluene was then stripped under vacuo at a maximum temperature of 60°C. Ethyl acetate was then added and was then stripped under vacuo at a maximum temperature of 60°C. To the semi solid oil was added tert-butyl methyl ether (2.5 liters) and the solution stirred overnight. The crystalline product was filtered off and washed with further tert-butyl methyl ether (0.3 liters). The mother liquors were concentrated and resubjected to silica chromatography (dissolved in 5 liters of toluene, added onto silica, eluted with 15 liters of toluene) and crystallized in the same fashion to afford a second crop. The product was isolated as a white crystalline solid. Yields range from 70% to 80%.

solution was redissolved in tetrahydrofuran (5 liter) for use in the next step. If storage was required, the tetrahydrofuran solution was stored and dried before use.

Preparation: 4: 2-Bromoacetyltetrahydrofuran

To a 20-liter glass vessel was added methylene chloride (10.0 liters) followed by acetyltetrahydrofuran (838.0 g, 7.34 moles). The solution was then cooled back to -10°C and triethylamine was added (854.0g, 8.44 moles). The vessel was purged with nitrogen and trimethylsilane triflate (1713.0 g, 7.71 moles) was added dropwise at a maximum temperature of -8°C. Addition was typically complete in 45 minutes. After 15 minutes stirring, a sample was removed for TLC and GC analysis, which showed that the reaction was completed. N-bromosuccinimide (1340g, 7.53 moles) was added to the solution at a maximum temperature of -5°C over a period of approximately 45 minutes in six portions. After a 30 minute stirring, the solution was sampled for GC and TLC analysis, which showed that the reaction was completed. The solution was then transferred to a 50-liter separating vessel, and 5% sodium bicarbonate (5 liters) was added with caution. The solution was stirred and separated. The upper aqueous phase was discarded, and the methylene chloride phase was washed with water, dried over sodium sulphate, filtered and stored in a freezer before use in the next step.

Preparation 5: Allyl-2-hydroxy-2-(3-benzyl-4-thia-2,6-diazabicyclo[3.2.0]hept-2-en-7-one)acetate

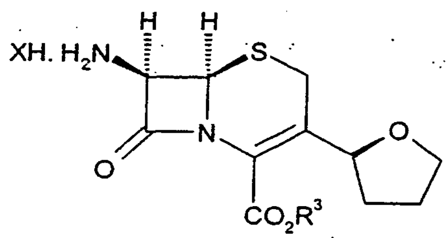
To a 50-liter glass vessel was added methylene chloride (20.6 liters) followed by 3-benzyl-4-thia-2,6-diazabicyclo[3.2.0]hept-2-en-7-one (1700 g, 7.79 moles). To this suspension was added allyl glyoxylate monohydrate (1285 g, 9.74 moles) followed by sufficient triethylamine (about 175 g) to bring the pH of the solution to 7.5-7.9. After a 1 hour stirring, the solution was sampled for TLC/HPLC analysis. Upon completion, the solution was quenched with 0.1 M of hydrochloric acid (2.75 liters) to a pH of 4.50-5.00. The upper aqueous phase was discarded, and the methylene chloride phase was washed with water (8 liters) and saturated sodium chloride (8 liters). The solution was dried over sodium sulphate and concentrated to a thick oil. The oil was dispersed in hexane (5 liters), filtered, and reslurried in tert-butyl methyl ether (5 liters) before filtration and washing with further tert-butyl methyl ether. Air drying afforded an off white crystalline product. Yields range from 72-99%.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. It is intended, therefore, that the invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.

mono-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di(C_{1-6}alkyl)phosphorothioate, (C_{1-6}alkyl)sulfonyl, mono-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, di-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, (C_{1-6}alkyl)-(CO)-S-, cyano-C_{1-6}alkoxy, C_{6-10}aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy and N-oxy-succinimidyl;

in the presence of a solvent, a base, an optional coupling agent and an optional catalyst.

2. The process according to claim 1 further comprising the step of preparing said compound of formula **II** by reacting a compound of formula **IV**:

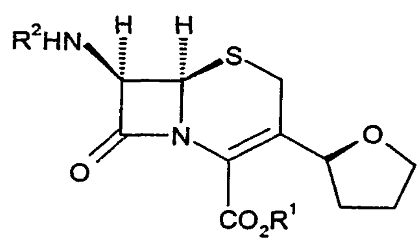


IV

wherein R^3 is para-nitrobenzyl or allyl; and X is halo;

with a suitable deprotecting agent; in the presence of a solvent.

3. A process for preparing a 3-cyclic-ether-substituted cephalosporin of the formula **I**:

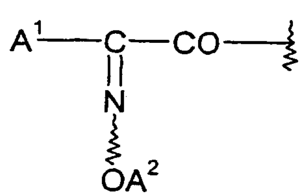


I

or a pharmaceutically acceptable salt thereof,

wherein the group CO_2R^1 is a carboxylic acid or a carboxylate salt; and

R^2 has the formula:



wherein

A^1 is selected from the group consisting of C_{6-10}aryl, C_{1-10}heteroaryl and C_{1-10}heterocyclyl;

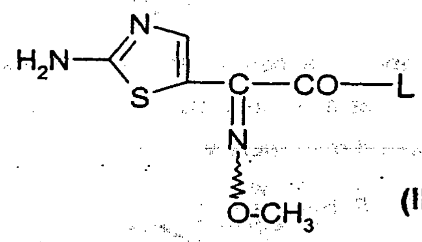
A^2 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{6-10}aryl, C_{1-6}alkyl(CO)(C_{1-6})alkyl-O-, HO(CO)(C_{1-6})alkyl, mono-(C_{6-10}aryl)(C_{1-6}alkyl), di-(C_{6-10}aryl)(C_{1-6}alkyl) and tri-(C_{6-10}aryl)(C_{1-6}alkyl);

in the presence of a solvent.

5. The process according to claim 1, wherein said A^1 moiety of said R^2 is aminothiazolyl, wherein said amino moiety of said aminothiazolyl is optionally protected;

said A^2 moiety of said R^2 is C_{1-6}alkyl;

said compound of formula **III** has the formula **IIIa**:



(IIIa)

wherein L is selected from the group consisting of halo, methanesulfonyl, diethylphosphorothioate and 3-benzthiazolyloxy.

6. A process according to claim 1, wherein said solvent is water, acetone, tetrahydrofuran, ethyl acetate, dimethylacetamide, dimethylformamide, acetonitrile, methylene chloride, 1,2-dichloroethane or mixtures thereof and said base is diisopropylethylamine or sodium hydroxide.

7. A process according to claim 1, wherein said process is performed in the presence of a catalyst and a coupling agent, wherein said catalyst is a Lewis acid catalyst selected from the group consisting of boron trihalide and aluminum halide; and wherein said coupling agent is selected from the group consisting of N,N'-diethylcarbodiimide, N,N'-dipropyl carbodiimide, N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide, N-ethyl-N'-[3-(dimethylamino)propyl]carbodiimide, N,N'-carbonyldiimidazole and N,N'-carbonyldithiazole.

8. A process according to claim 2, wherein said X is chloro.

9. A process according to claim 2, wherein said R^3 is para-nitrobenzyl, said suitable deprotecting agent is sodium dithionite or a catalytic hydrogenating agent, and said solvent is acetone, water, tetrahydrofuran or mixtures thereof.

10. A process according to claim 3, wherein said R^3 is allyl and said suitable deprotecting agent is tetrakistriphenyl phosphine palladium (0).

11. A process according to claim 4, wherein said solvent is methylene chloride, tetrahydrofuran or mixtures thereof.

12. A compound of formula **II**:

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/02225

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D501/06 C07D501/18 C07D501/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 92 01695 A (BEECHAM GROUP PLC) 6 February 1992 (1992-02-06) claims; examples & US 6 001 997 A 14 December 1999 (1999-12-14) cited in the application	1-3, 12-15
Y	WO 96 17847 A (PFIZER ;BURTON GEORGE (GB); NAYLOR ANTOINETTE (GB)) 13 June 1996 (1996-06-13) page 11 -page 13; claims; examples	1-3, 12-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL – 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Chouly, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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